

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
12 July 2007 (12.07.2007)

PCT

(10) International Publication Number  
**WO 2007/079146 A1**

(51) International Patent Classification:  
*A61K 31/47* (2006.01)    *A61P 35/02* (2006.01)  
*A61K 31/4188* (2006.01)

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS,  
JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS,  
LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY,  
MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS,  
RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,  
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(21) International Application Number:  
PCT/US2006/049431

(22) International Filing Date:  
28 December 2006 (28.12.2006)

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIGO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/754,424      28 December 2005 (28.12.2005) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2007/079146 A1

(54) Title: TREATMENT FOR NON-HODGKIN'S LYMPHOMA

(57) Abstract: The present invention provides a method of treating Non-Hodgkin's lymphoma. Generally, the method includes administering to a patient with Non-Hodgkin's lymphoma an amount of a TLR agonist compound effective to ameliorate at least one symptom or clinical sign of Non-Hodgkin's lymphoma.

## TREATMENT FOR NON-HODGKIN'S LYMPHOMA

### Background

5        There has been a major effort in recent years, with significant success, to discover new drug compounds that act by stimulating certain key aspects of the immune system, as well as by suppressing certain other aspects (see, e.g., U.S. Pat. Nos. 6,039,969 and 6,200,592). These compounds appear to act through basic immune system mechanisms known as Toll-like receptors (TLRs) and are referred to herein as "TLR agonists."

10      Certain TLR agonists, known as "immune response modifiers" (IRMs) may be useful for treating a wide variety of diseases and conditions by inducing selected cytokine biosynthesis, induction of co-stimulatory molecules, and/or increasing antigen-presenting capacity. For example, certain IRM compounds are known to provide effective immunotherapy for treating certain viral diseases (e.g., human papilloma virus, hepatitis, herpes), certain neoplasias (e.g., basal cell carcinoma, squamous cell carcinoma, actinic keratosis, melanoma), certain TH2-mediated diseases (e.g., asthma, allergic rhinitis, atopic dermatitis), certain auto-immune diseases (e.g., multiple sclerosis), and are also useful as vaccine adjuvants.

20      Many of the TLR agonists are small organic molecule imidazoquinoline amine derivatives (see, e.g., U.S. Pat. No. 4,689,338), but a number of other compound classes are known as well (see, e.g., U.S. Pat. Nos. 5,446,153; 6,194,425; and 6,110,929; and International Publication Number WO 2005/079195) and more are still being discovered. Other IRMs have higher molecular weights, such as oligonucleotides, including CpGs (see, e.g., U.S. Pat. No. 6,194,388).

25      In view of the great therapeutic potential for TLR agonists, and despite the important work that has already been done, there is a substantial ongoing need to expand their uses and therapeutic benefits.

### Summary

30      It has been found that certain small molecule TLR agonists can be used to treat Non-Hodgkin's lymphoma. Accordingly, the present invention provides a method of treating Non-Hodgkin's lymphoma. Generally, the method includes administering to a

patient with Non-Hodgkin's lymphoma an amount of a Toll-like receptor (TLR) agonist compound effective to ameliorate at least one symptom or clinical sign of Non-Hodgkin's lymphoma. In some cases, the method may be used to treat Non-Hodgkin's lymphoma that has not responded to standard chemotherapy, radiotherapy, bone marrow transplant therapy, or immunotherapy.

5 Various other features and advantages of the present invention should become readily apparent with reference to the following detailed description, examples, claims and appended drawings. In several places throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

10

#### Detailed Description of Illustrative Embodiments of the Invention

The present invention provides methods of treating a patient with Non-Hodgkin's lymphoma. Generally, the method includes administering to the patient a drug in an amount and for a time sufficient to provide some relief from the disease. In some cases, 15 the treatment may even cause complete remission of the disease. In some cases, the invention can provide effective treatment to patients that have failed to benefit from other forms of treatment.

As used herein, the following terms shall have the indicated meanings:

20 “Agonist” refers to a compound that can combine with a receptor (e.g., a TLR) to induce a cellular activity. An agonist may be a ligand that directly binds to the receptor. Alternatively, an agonist may combine with a receptor indirectly by, for example, (a) forming a complex with another molecule that directly binds to the receptor, or (b) otherwise results in the modification of another compound so that the other compound 25 directly binds to the receptor. An agonist may be referred to as an agonist of a particular TLR (e.g., a TLR7 agonist) or a particular combination of TLRs (e.g., a TLR 7/8 agonist – an agonist of both TLR7 and TLR8).

“Ameliorate” refers to any reduction in the extent, severity, frequency, and/or likelihood of a symptom or clinical sign characteristic of a particular condition.

30 “Sign” or “clinical sign” refers to an objective physical finding relating to a particular condition capable of being found by one other than the patient.

“Symptom” refers to any subjective evidence of disease or of a patient's condition.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably. Thus, for example, a formulation comprising "a" TLR agonist can be interpreted to mean that the formulation includes at least one (i.e., one or more) TLR agonist.

5 Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.).

Non-Hodgkin's lymphoma is a collection of more than a dozen different cancers of the lymphatic system. The lymphatic system includes lymph nodes, spleen, and other organs of the immune system and helps to generate the body's immune defenses.

10 Generally, there are two kinds of lymphomas: Hodgkin's lymphoma and non-Hodgkin's lymphoma.

Symptoms associated with Non-Hodgkin's lymphoma can vary widely, depending on the portion of the lymphatic system in which the cancer develops. The most common symptom is a noticeable, usually painless swelling of a lymph node. Non-Hodgkin's  
15 lymphoma in the digestive tract can cause nausea, vomiting, or abdominal pain; in the chest, shortness of breath or cough may develop. If the brain is involved, patients may have headaches, vision changes, or seizures. If the bone marrow is affected, lymphoma cells may crowd out red blood cell precursors, causing anemia. Reddened patches on the skin can occur when lymphoma cells there prompt localized inflammation. Fever,  
20 excessive sweating (with night sweats), fatigue, widespread itching, and unintentional weight loss are also common symptoms.

Non-Hodgkin's lymphoma is usually diagnosed after a biopsy from the patient is examined and the cancer cells are identified. The type of Non-Hodgkin's lymphoma may often be determined by the appearance of the cancer cells and/or by identifying certain  
25 characteristic proteins on the surfaces of the cancer cells.

Non-Hodgkin's lymphomas are classed as low-, intermediate- and high-grade. This classification scheme accurately predicts the survival of untreated patients, but is not as reliable in predicting outcome after treatment. Low-grade lymphomas are slow-growing tumors, and some patients can survive for more than a decade without treatment. Although  
30 chemotherapy often can shrink low-grade lymphomas, the cancer often recurs within five years. Recurrent tumors can also be treated with chemotherapy or radiation, but over time, low-grade Non-Hodgkin's lymphomas tend to become more aggressive and less

responsive to therapy. Consequently, these types of lymphomas are not easily cured using currently available treatments.

In contrast, intermediate-grade and high-grade lymphomas are fast-growing tumors that, without treatment, generally are fatal within a year or two of diagnosis.

5 Chemotherapy may cure many types of these lymphomas.

Patients with more aggressive or resistant disease may require more intensive treatment. High-dose chemotherapy with bone marrow transplantation may be a treatment option in selected cases.

10 Treatment of any particular Non-Hodgkin's lymphoma may depend on the type of tumor, the stage of the disease, and the patient's age and general health. Most patients receive chemotherapy, radiation therapy, or both.

15 Treatment of low-grade Non-Hodgkin's lymphoma may be postponed until the cancer shows signs of spreading, or causes systemic symptoms (such as fevers or weight loss), or until the tumors become excessively bulky or threaten vital organs such as the kidneys or lungs. Delaying treatment often does not adversely affect long-term survival and may improve a patient's quality of life, as the treatments themselves can be debilitating. Some patients with low-grade Non-Hodgkin's lymphoma have spontaneous remissions, although these disease-free periods rarely last for long.

20 Chemotherapy for Non-Hodgkin's lymphoma usually involves several different drugs given at the same time. Some drugs commonly used to treat Non-Hodgkin's lymphoma include, for example, chlorambucil, cyclophosphamide, doxorubicin, vincristine, and mitoxantrone. Anti-inflammatory drugs such as, for example, prednisone also may be included in a treatment plan.

25 Radiation therapy uses high-energy x-rays to damage cancer cells and stop their growth. Radiation therapy is directed to the areas of the body known to harbor cancer cells.

30 A Non-Hodgkin's lymphoma patient with a poor prognosis may be a candidate for high-dose chemotherapy, with or without radiation, followed by a bone marrow transplant. Before therapy, a portion of the patient's bone marrow may be extracted, treated in an attempt to purge any cancer cells and then returned to the patient after the patient completes the chemotherapy. Bone marrow transplants can improve the long-term

survival of patients with intermediate- or high-grade lymphomas that have relapsed but are still sensitive to chemotherapy.

Non-Hodgkin's lymphoma also may be treated using immunotherapy. One form of immunotherapy uses monoclonal antibodies that bind to antigens that are unique to lymphoma cells. The antibodies may be attached to radioactive compounds or toxins that kill cells. Monoclonal antibody therapy is designed to more selectively target cancer cells, resulting in less severe side effects than standard chemotherapy. Other immunotherapies include administration of certain cytokines such as, for example, IL-2 and/or IFN- $\alpha$  in combination with standard chemotherapy or radiation therapies.

With the present invention, patients now have an additional treatment option. Certain TLR agonists have been determined to be useful for treating Non-Hodgkin's lymphoma. Administering a TLR agonist to a patient with Non-Hodgkin's lymphoma can reduce the extent and/or severity of symptoms of the disease. In some cases, treatment with a TLR agonist can provide a partial response. In other cases, treatment with a TLR agonist may provide a complete response. For some patients, treatment with a TLR agonist may provide effective treatment even after either (a) the Non-Hodgkin's lymphoma has failed to respond to standard chemotherapy, radiotherapy, or bone marrow transplant therapy, or (b) after initially responding to standard therapy, the Non-Hodgkin's lymphoma relapses.

Certain TLR agonists are small organic molecules (e.g., molecular weight under about 1000 Daltons, preferably under about 500 Daltons, as opposed to large biological molecules such as proteins, peptides, and the like) such as those disclosed in, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,389,640; 5,446,153; 5,482,936; 5,756,747; 6,110,929; 6,194,425; 6,331,539; 6,376,669; 6,451,810; 6,525,064; 6,541,485; 6,545,016; 6,545,017; 6,573,273; 6,656,938; 6,660,735; 6,660,747; 6,664,260; 6,664,264; 6,664,265; 6,667,312; 6,670,372; 6,677,347; 6,677,348; 6,677,349; 6,683,088; 6,756,382; 6,797,718; 6,818,650; and 7,7091,214; U.S. Patent Publication Nos. 2004/0091491, 2004/0176367, and 2006/0100229; and International Publication Nos. WO 2005/18551, WO 2005/18556, WO 2005/20999, WO 2005/032484, WO 2005/048933, WO 2005/048945, WO 2005/051317, WO 2005/051324, WO 2005/066169, WO 2005/066170, WO 2005/066172, WO 2005/076783, WO 2005/079195, WO 2005/094531, WO 2005/123079, WO 2005/123080, WO 2006/009826, WO

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2006/086634, WO 2006/091567, WO 2006/091568, WO 2006/091647, WO 2006/093514,  
5 and WO 2006/098852.

Additional examples of small molecule IRMs include certain purine derivatives  
(such as those described in U.S. Patent Nos. 6,376,501, and 6,028,076), certain  
imidazoquinoline amide derivatives (such as those described in U.S. Patent No.  
6,069,149), certain imidazopyridine derivatives (such as those described in U.S. Patent  
10 No. 6,518,265), certain benzimidazole derivatives (such as those described in U.S. Patent  
6,387,938), certain derivatives of a 4-aminopyrimidine fused to a five membered nitrogen  
containing heterocyclic ring (such as adenine derivatives described in U. S. Patent Nos.  
6,376,501; 6,028,076 and 6,329,381; and in WO 02/08905), and certain 3- $\beta$ -D-  
ribofuranosylthiazolo[4,5-d]pyrimidine derivatives (such as those described in U.S.  
15 Publication No. 2003/0199461), and certain small molecule immuno-potentiator  
compounds such as those described, for example, in U.S. Patent Publication No.  
2005/0136065.

Other TLR agonists include large biological molecules such as oligonucleotide  
sequences. Some TLR agonist oligonucleotide sequences contain cytosine-guanine  
20 dinucleotides (CpG) and are described, for example, in U.S. Patent Nos. 6,194,388;  
6,207,646; 6,239,116; 6,339,068; and 6,406,705. Some CpG-containing oligonucleotides  
can include synthetic immunomodulatory structural motifs such as those described, for  
example, in U.S. Patent Nos. 6,426,334 and 6,476,000. Other TLR agonist nucleotide  
sequences lack CpG sequences and are described, for example, in International Patent  
25 Publication No. WO 00/75304. Still other TLR agonist nucleotide sequences include  
guanosine- and uridine-rich single-stranded RNA (ssRNA) such as those described, for  
example, in Heil *et al.*, *Science*, vol. 303, pp. 1526-1529, March 5, 2004.

Other TLR agonists include biological molecules such as aminoalkyl  
glucosaminide phosphates (AGPs) and are described, for example, in U.S. Patent Nos.  
30 6,113,918; 6,303,347; 6,525,028; and 6,649,172.

Unless otherwise indicated, reference to a compound can include the compound in  
any pharmaceutically acceptable form, including any isomer (e.g., diastereomer or

enantiomer), salt, solvate, polymorph, and the like. In particular, if a compound is optically active, reference to the compound can include each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

In some embodiments of the present invention, the TLR agonist may be an agonist of at least one TLR such as, for example, an agonist of TLR7 or TLR8. The IRM may also in some cases be an agonist of TLR 9. In some embodiments, the TLR agonist is an agonist of TLR7. A suitable TLR7 agonist may be an agonist of one or more additional TLRs—i.e., also an agonist of TLR8, a so-called TLR7/8 agonist. Alternatively, the TLR7 agonist may be a TLR7-selective agonist. As used herein, the term "TLR7-selective agonist" refers to a compound that acts as an agonist of TLR7, but does not act as an agonist of TLR8.

A TLR8-selective agonist or a TLR7-selective agonist may act as an agonist for the indicated TLR and one or more of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR9, or TLR10. Accordingly, while "TLR8-selective agonist" may refer to a compound that acts as an agonist for TLR8 and for no other TLR, it may alternatively refer to a compound that acts as an agonist of TLR8 and, for example, TLR6. Similarly, "TLR7-selective agonist" may refer to a compound that acts as an agonist for TLR7 and for no other TLR, but it may alternatively refer to a compound that acts as an agonist of TLR7 and, for example, TLR6.

The TLR agonism for a particular compound may be assessed in any suitable manner. For example, assays and recombinant cell lines suitable for detecting TLR agonism of test compounds are described, for example, in U.S. Patent Publication Nos. US2004/0014779, US2004/0132079, US2004/0162309, US2004/0171086, US2004/0191833, and US2004/0197865.

Regardless of the particular assay employed, a compound can be identified as an agonist of a particular TLR if performing the assay with a compound results in at least a threshold increase of some biological activity mediated by the particular TLR. Conversely, a compound may be identified as not acting as an agonist of a specified TLR if, when used to perform an assay designed to detect biological activity mediated by the specified TLR, the compound fails to elicit a threshold increase in the biological activity. Unless otherwise indicated, an increase in biological activity refers to an increase in the same biological activity over that observed in an appropriate control. An assay may or

may not be performed in conjunction with the appropriate control. With experience, one skilled in the art may develop sufficient familiarity with a particular assay (e.g., the range of values observed in an appropriate control under specific assay conditions) that performing a control may not always be necessary to determine the TLR agonism of a compound in a particular assay.

The precise threshold increase of TLR-mediated biological activity for determining whether a particular compound is or is not an agonist of a particular TLR in a given assay may vary according to factors known in the art including but not limited to the biological activity observed as the endpoint of the assay, the method used to measure or detect the endpoint of the assay, the signal-to-noise ratio of the assay, the precision of the assay, and whether the same assay is being used to determine the agonism of a compound for two or more TLRs. Accordingly it is not practical to set forth generally the threshold increase of TLR-mediated biological activity required to identify a compound as being an agonist or a non-agonist of a particular TLR for all possible assays. Those of ordinary skill in the art, however, can readily determine the appropriate threshold with due consideration of such factors.

Assays employing HEK293 cells transfected with an expressible TLR structural gene may use a threshold of, for example, at least a three-fold increase in a TLR-mediated biological activity (e.g., NF $\kappa$ B activation) when the compound is provided at a concentration of, for example, from about 1  $\mu$ M to about 10  $\mu$ M for identifying a compound as an agonist of the TLR transfected into the cell. However, different thresholds and/or different concentration ranges may be suitable in certain circumstances. Also, different thresholds may be appropriate for different assays.

In some embodiments of the present invention, the TLR agonist may be a small molecule (e.g., molecular weight of less than about 1000 Daltons) TLR agonist.

In some embodiments of the present invention, the TLR agonist may include a 2-aminopyridine fused to a five membered nitrogen-containing heterocyclic ring, or a 4-aminopyrimidine fused to a five membered nitrogen-containing heterocyclic ring.

TLR agonists having a 2-aminopyridine fused to a five membered nitrogen-containing heterocyclic ring include, for example, imidazoquinoline amines including but not limited to substituted imidazoquinoline amines such as, for example, amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea

substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines, heterocyclic ether substituted imidazoquinoline amines, amido ether substituted imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines,  
5 hydroxylamine substituted imidazoquinoline amines, oxime substituted imidazoquinoline amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted imidazoquinoline amines, and imidazoquinoline diamines; tetrahydroimidazoquinoline amines including but not limited to amide substituted tetrahydroimidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted  
10 tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, hydroxylamine substituted  
15 tetrahydroimidazoquinoline amines, oxime substituted tetrahydroimidazoquinoline amines, and tetrahydroimidazoquinoline diamines; imidazopyridine amines including but not limited to amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido  
20 ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, and thioether substituted imidazopyridine amines; 1,2-bridged imidazoquinoline amines; 6,7-fused cycloalkylimidazopyridine amines; imidazonaphthyridine amines; tetrahydroimidazonaphthyridine amines;  
oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines;  
25 thiazolopyridine amines; oxazolonaphthyridine amines; thiazolonaphthyridine amines; pyrazolopyridine amines; pyrazoloquinoline amines; tetrahydropyrazolopyridine amines; pyrazolonaphthyridine amines; tetrahydropyrazolonaphthyridine amines; and 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines.  
30 In certain embodiments, the TLR agonist may be an imidazonaphthyridine amine, a tetrahydroimidazonaphthyridine amine, an oxazoloquinoline amine, a thiazoloquinoline amine, an oxazolopyridine amine, a thiazolopyridine amine, an oxazolonaphthyridine

amine, a thiazolonaphthyridine amine, a pyrazolopyridine amine, a pyrazoloquinoline amine, a tetrahydropyrazoloquinoline amine, a pyrazolonaphthyridine amine, or a tetrahydropyrazolonaphthyridine amine.

In certain embodiments, the TLR agonist may be a substituted imidazoquinoline amine, a tetrahydroimidazoquinoline amine, an imidazopyridine amine, a 1,2-bridged imidazoquinoline amine, a 6,7-fused cycloalkylimidazopyridine amine, an imidazonaphthyridine amine, a tetrahydroimidazonaphthyridine amine, an oxazoloquinoline amine, a thiazoloquinoline amine, an oxazolopyridine amine, a thiazolopyridine amine, an oxazolonaphthyridine amine, a thiazolonaphthyridine amine, a pyrazolopyridine amine, a pyrazoloquinoline amine, a tetrahydropyrazoloquinoline amine, 10 a pyrazolonaphthyridine amine, or a tetrahydropyrazolonaphthyridine amine.

As used herein, a substituted imidazoquinoline amine refers to an amide substituted imidazoquinoline amine, a sulfonamide substituted imidazoquinoline amine, a urea substituted imidazoquinoline amine, an aryl ether substituted imidazoquinoline amine, a heterocyclic ether substituted imidazoquinoline amine, an amido ether substituted imidazoquinoline amine, a sulfonamido ether substituted imidazoquinoline amine, a urea substituted imidazoquinoline ether, a thioether substituted imidazoquinoline amine, a hydroxylamine substituted imidazoquinoline amine, an oxime substituted imidazoquinoline amine, a 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted imidazoquinoline amine, or an imidazoquinoline diamine. As used herein, substituted imidazoquinoline amines specifically and expressly exclude 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine and 4-amino- $\alpha,\alpha$ -dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-ethanol.

In one embodiment, the TLR agonist is a sulfonamide substituted imidazoquinoline amine such as, for example, N-[4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide or N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide.

Suitable TLR agonists also may include the purine derivatives, imidazoquinoline amide derivatives, benzimidazole derivatives, adenine derivatives, aminoalkyl glucosaminide phosphates, small molecule immuno-potentiator compounds, and oligonucleotide sequences described above.

The TLR agonist may be provided in any formulation suitable for contacting cells *in vitro* or administering to a subject. Suitable types of formulations are described, for example, in U.S. Pat. No. 5,238,944; U.S. Pat. No. 5,939,090; U.S. Pat. No. 6,245,776; European Patent No. EP 0 394 026; U.S. Patent Publication No. 2003/0199538; and 5 International Patent Publication Nos. WO 2006/073940 and WO 2006/074045. The compound may be provided in any suitable form including but not limited to a solution, a suspension, an emulsion, or any form of mixture. The compound may be delivered in formulation with any pharmaceutically acceptable excipient, carrier, or vehicle.

A formulation containing a TLR agonist may be administered in any suitable 10 manner such as, for example, non-parenterally or parenterally. As used herein, non-parenterally refers to administration through the digestive tract, including by oral ingestion. Parenterally refers to administration other than through the digestive tract such as, for example, intravenously, intramuscularly, transdermally, subcutaneously, transmucosally (e.g., by inhalation), or topically.

15 The composition of a formulation suitable for practicing the invention will vary according to factors known in the art including but not limited to the physical and chemical nature of the TLR agonist, the nature of the carrier, the intended dosing regimen, the state of the subject's immune system (e.g., suppressed, compromised, stimulated), and the method of administering the TLR agonist. Accordingly, it is not practical to set forth 20 generally the composition of a formulation effective for treating Non-Hodgkin's lymphoma for all possible applications. Those of ordinary skill in the art, however, can readily determine an appropriate formulation with due consideration of such factors.

In some embodiments, the methods of the present invention include administering 25 a TLR agonist to a patient in a formulation of, for example, from about 0.001% to about 20% (unless otherwise indicated, all percentages provided herein are weight/weight with respect to the total formulation) to the subject, although in some embodiments the TLR agonist may be administered using a formulation that provides TLR agonist in a concentration outside of this range. In certain embodiments, the method includes administering to a patient a formulation that includes from about 0.01% to about 0.5% 30 TLR agonist. In one exemplary embodiment, the formulation includes about 0.2% TLR agonist.

Typically, the TLR agonist will be administered to a patient as part of a treatment plan that considers the amount of TLR agonist administered per dose, the frequency of administering the TLR agonist, and the duration of the time period over which the TLR agonist will be administered. Often, a treatment plan is devised that seeks to administer  
5 the TLR agonist in the greatest dose tolerable by the patient. If a given dose is considered not well tolerated by the patient, the first recourse may be to provide prophylactic treatment for side effects of the TLR agonist in order to maintain dose strength, frequency, and duration. If prophylactic treatment fails to make a given dose tolerable, then the dose strength, frequency, and/or duration of the treatment plan may be modified as appropriate.

10 An amount of a TLR agonist effective for treating Non-Hodgkin's lymphoma is an amount to ameliorate at least one symptom or clinical sign of the disease. In some embodiments, this may be an amount that causes a decrease in the extent or severity of one of the symptoms or clinical signs of the disease, examples of which are described above. In other embodiments, this may be an amount to generate a partial response, as defined  
15 below. In still other embodiments, this may be an amount sufficient to cause remission of the Non-Hodgkin's lymphoma, defined herein as a complete response and/or a clinical complete response defined below.

20 The precise amount of TLR agonist for treating Non-Hodgkin's lymphoma may vary according to factors known in the art including but not limited to the physical and chemical nature of the TLR agonist, the nature of the carrier, the intended dosing regimen, the state of the subject's immune system (e.g., suppressed, compromised, stimulated), the method of administering the TLR agonist, and the patient's tolerance of the TLR agonist. Accordingly, it is not practical to set forth generally the amount that constitutes an amount of TLR agonist effective for treating Non-Hodgkin's lymphoma for all possible patients.  
25 Those of ordinary skill in the art, however, can readily determine the appropriate amount with due consideration of such factors.

In some embodiments, the methods of the present invention include administering sufficient TLR agonist to provide a dose of, for example, from about 0.01 mg/m<sup>2</sup> to about 5.0 mg/m<sup>2</sup> to the patient, although in some embodiments the methods may be performed  
30 by administering TLR agonist in a dose outside this range. In some of these embodiments, the method includes administering sufficient TLR agonist to provide a dose of from about

0.1 mg/m<sup>2</sup> to about 2.0 mg/m<sup>2</sup> to the patient, for example, a dose of from about 0.4 mg/m<sup>2</sup> to about 1.2 mg/m<sup>2</sup>.

The dose may be calculated using actual body weight obtained just prior to the beginning of the treatment course. For the dosages provided herein, body surface area (m<sup>2</sup>) is calculated prior to the beginning of the treatment course using the Dubois method: m<sup>2</sup> = (wt kg<sup>0.425</sup> x height cm<sup>0.725</sup>) x 0.007184.

In one embodiment, the starting dose for a patient may be, for example, 0.6 mg/m<sup>2</sup>. In another embodiment, the starting dose for a patient may be, for example, 1.0 mg/m<sup>2</sup>. If a dose is well tolerated by the patient after two consecutive administrations at a given dose, the dose may be increased by an appropriate amount such as, for example, by 0.2 mg/m<sup>2</sup>. In some embodiments, the dosage may be increased in this manner up to a maximum dose of about 1.2 mg/m<sup>2</sup>. In other embodiments, the dosage may be increased up to a maximum dose of about 2.0 mg/m<sup>2</sup>. Also, if any dose is not well tolerated by a patient, the next dose may be decreased by an appropriate amount such as, for example, by 0.2 mg/m<sup>2</sup> until the dose is tolerated by the patient. In some embodiments, the dosage may be decreased in this manner down to a minimum dose of about 0.4 mg/m<sup>2</sup>.

The dosing regimen may depend at least in part on many factors known in the art including but not limited to the physical and chemical nature of the TLR agonist, the nature of the carrier, the amount of TLR agonist being administered, the state of the subject's immune system (e.g., suppressed, compromised, stimulated), the method of administering the TLR agonist, and the patient's tolerance of the TLR agonist. Accordingly it is not practical to set forth generally the dosing regimen effective for treating Non-Hodgkin's lymphoma for all patients. Those of ordinary skill in the art, however, can readily determine an appropriate dosing regimen with due consideration of such factors.

In some embodiments of the invention, the TLR agonist may be administered, for example, from a single dose to a series of about 36 doses, although in some embodiments the methods of the present invention may be performed by administering the TLR agonist at a frequency outside this range. In certain embodiments, the TLR agonist may be administered from about six doses to about 24 doses, such as, for example, from about 12 doses to about 24 doses.

Typically, a treatment plan will be developed that includes an intended total number of doses to be administered over a prescribed period of time. However, the goal of a treatment plan usually is to optimize dosing based on individual patient response and tolerability. Thus, if deemed appropriate, one or more rest periods may be incorporated into a treatment plan, while retaining the total dose goal—e.g., a total of 24 doses in a treatment plan that includes dosing two times per week for 12 weeks. A rest period may be defined as no TLR agonist administered over a seven day interval, and may be implemented if a patient does not tolerate a dose. In a typical treatment plan, a patient may be allowed to have a specified number of rest periods among a specified number of doses. As one example, a treatment plan may allow rest periods as needed to continue on therapy, up to a maximum of two rest periods (i.e., two weeks without receiving TLR agonist) per eight doses administered.

In one embodiment, a treatment plan may include administration of the TLR agonist two times per week for 12 weeks, a total of 24 doses. Such a treatment plan may permit, for example, six rest periods (two rest periods per eight doses).

If a patient does not tolerate a given dose well, the patient may receive prophylactic treatment to aid tolerability rather than reducing the dose of TLR agonist or implementing a rest period. For example, fever or flu-like symptoms may be treated with analgesics and/or antipyretics such as, for example, acetaminophen, or non-steroidal anti-inflammatory drugs (NSAIDs) such as, for example, naproxen or ibuprofen, as appropriate. Alternatively, certain corticosteroids such as, for example, prednisone, may be used to increase tolerability of the TLR agonist without delaying treatment or reducing the dose of TLR agonist being administered.

Additionally, a treatment plan may include combination therapy—i.e., TLR agonist therapy in combination with, for example, chemotherapy, immunotherapy, or radiotherapy. Each component therapy (i.e., TLR agonist therapy, chemotherapy and/or immunotherapy) may itself include a combination of therapeutic agents within that particular class. Thus, a combination therapy may include, for example, one or more TLR agonists, one or more chemotherapeutic agents and/or one or more immunotherapeutic agents. Components of the combination therapy may be provided together in a single formulation, if appropriate. In most cases, however, combination therapy will involve administration of multiple therapeutic formulations.

In the absence of progressive disease and if there is no unacceptable toxicity, one or more additional treatment plans may be initiated. A two to eight week treatment-free interval may be imposed between treatment courses for recovery, if needed.

A complete response may be defined as a patient achieving a complete regression  
5 for at least four weeks of all palpable and x-ray demonstrable disease and bone marrow disease judged by unilateral iliac crest bone marrow biopsy (if such as biopsy was initially positive). Lymph nodes remaining in areas of previous known disease may be considered to be uninvolved if they measure less than about 1.0 cm x 1.0 cm. A patient may still be a complete responder having lymph nodes larger size if other criteria are met. For example,  
10 a patient may still be considered a complete responder with lymph nodes greater than about 1.0 cm x 1.0 cm if the larger lymph nodes are documented to be free of tumor on biopsy, or have failed to enlarge over three months off-therapy. In some embodiments, if the patient's liver and/or spleen are enlarged prior to onset of treatment, the enlarged organ should return to normal size in order for the patient to be considered a complete responder.  
15 In embodiments in which the patient began treatment after having a liver biopsy showing cancer in the liver (i.e., a positive liver biopsy), a negative liver biopsy, indicating complete remission of the cancer in the liver, may be required for the patient to be considered a complete responder.

A partial response may be defined in a patient who has not achieved a complete  
20 response, but has shown a response to therapy with a 50% or greater reduction in the sum of the products of the dimensions of the measurable lesions for at least four weeks. In embodiments in which the liver contains an indicator lesion, a decrease of at least 50% in the sum of the measurements below the right costal margin, xiphoid process, and left costal margin may define a partial responder. In embodiments in which the spleen was  
25 enlarged prior to therapy, various definitions of a partial responder may be appropriate. For example, if the enlarged spleen prior to treatment measured less than 5 cm below the costal margin, a partial response may be considered to have occurred if the spleen returns to normal size; if the spleen measured greater than 5 cm below the costal margin prior to treatment, a decrease in size by at least 50% may define a partial responder.

30

Examples

The following examples have been selected merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however, that while the examples serve this purpose, the particular materials and amounts used as well as other conditions and details are not to be construed in a matter that would unduly limit the scope of this invention.

5 The drug used in the examples is the TLR agonist N-[4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide, which is a sulfonamide substituted imidazoquinoline amine, the synthesis of which is described, for example, at U.S. Pat. No. 6,677,349, Example 236.

10 The drug is provided in a sterile 0.2% injectable solution in glass ampoules. One mL of the 0.2% solution corresponds to 2 mg of drug. Each mL of solution contains the following inactive ingredients: 4.2 mg citric acid and 45 mg mannitol in USP Water for Injection, adjusted to pH 5 with sodium hydroxide. The solution is stored at room temperature (15 to 30°C) and protected from light during storage.

15

#### **Example 1**

A 12-year-old male having hepatosplenic gamma/delta T-cell lymphoma received a bone marrow transplant January 2006. On April 7, 2006, the patient relapsed, having 32% lymphoma cells.

20 The patient began therapy using the 0.2% TLR agonist solution described above on April 10, 2006. White blood cell count, absolute neutrophil count (ANC) and hemoglobin all improved with TLR agonist treatment.

25

The complete disclosures of the patents, patent documents and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. In case of conflict, the present specification, including definitions, shall control.

Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention.

30

Illustrative embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

What is claimed is:

1. A method of treating Non-Hodgkin's lymphoma, the method comprising:  
administering to a patient with Non-Hodgkin's lymphoma an amount of a Toll-like receptor (TLR) agonist compound effective to ameliorate at least one symptom or  
5 clinical sign of Non-Hodgkin's lymphoma.
- 10 2. The method of claim 1 wherein the TLR agonist comprises an imidazoquinoline amine, a tetrahydroimidazoquinoline amine, an imidazopyridine amine, a 1,2-bridged imidazoquinoline amine, a 6,7-fused cycloalkylimidazopyridine amine, an imidazonaphthyridine amine, a tetrahydroimidazonaphthyridine amine, an oxazoloquinoline amine, a thiazoloquinoline amine, an oxazolopyridine amine, a thiazolopyridine amine, an oxazolonaphthyridine amine, a thiazolonaphthyridine amine, a pyrazolopyridine amine, a pyrazoloquinoline amine, a tetrahydropyrazoloquinoline amine, a pyrazolonaphthyridine amine, or a tetrahydropyrazolonaphthyridine amine.  
15 3. The method of claim 1 wherein the TLR agonist comprises a substituted imidazoquinoline amine.
- 20 4. The method of claim 3 wherein the TLR agonist comprises an amide substituted imidazoquinoline amine, a sulfonamide substituted imidazoquinoline amine, a urea substituted imidazoquinoline amine, an aryl ether substituted imidazoquinoline amine, a heterocyclic ether substituted imidazoquinoline amine, an amido ether substituted imidazoquinoline amine, a sulfonamido ether substituted imidazoquinoline amine, a urea substituted imidazoquinoline ether, a thioether substituted imidazoquinoline amine, a  
25 hydroxylamine substituted imidazoquinoline amine, an oxime substituted imidazoquinoline amine, a 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted imidazoquinoline amine, or an imidazoquinoline diamine.
- 30 5. The method of claim 4 wherein the TLR agonist comprises a sulfonamide substituted imidazoquinoline amine.

6. The method of claim 1 wherein the TLR agonist comprises a sulfonamide substituent.

7. The method of claim 1 wherein the TLR agonist comprises an agonist of at least 5 one Toll-like receptor (TLR).

8. The method of claim 7 wherein the TLR agonist comprises an agonist of at least TLR7.

10 9. The method of claim 1 wherein the TLR agonist is administered systemically.

10. The method of claim 9 wherein the TLR agonist is administered subcutaneously or intravenously.

15 11. The method of claim 1 wherein the TLR agonist is administered at least once per week.

12. The method of claim 11 wherein the TLR agonist is administered at least twice per week.

20 13. The method of claim 1 wherein the TLR agonist is administered for at least three weeks.

25 14. The method of claim 13 wherein the TLR agonist is administered for at least six weeks.

15. The method of claim 14 wherein the TLR agonist is administered for at least 12 weeks.

30 16. The method of claim 1 wherein the TLR agonist is administered until the Non-Hodgkin's lymphoma is in remission.

17. The method of claim 1 wherein the TLR agonist is provided in a dose of at least 0.4 mg/m<sup>2</sup>.

18. The method of claim 17 wherein the TLR agonist is provided in a dose of at least 5 0.6 mg/m<sup>2</sup>.

19. The method of claim 18 wherein the TLR agonist is provided in a dose of at least 1.0 mg/m<sup>2</sup>.

10 20. The method of claim 1 wherein the TLR agonist is provided in a dose of no more than 2.0 mg/m<sup>2</sup>.

21. The method of claim 1 wherein the TLR agonist is provided in a dose of no more than 1.2 mg/m<sup>2</sup>.

15 22. The method of claim 1 wherein the Non-Hodgkin's lymphoma has not responded to another therapy.

20 23. The method of claim 1 wherein the Non-Hodgkin's lymphoma has relapsed after treatment with another therapy.

24. The method of claim 1 further comprising administering to the patient a chemotherapeutic agent or an immunotherapeutic agent.

25 25. Use of a TLR agonist in the manufacture of a pharmaceutical composition for treating Non-Hodgkin's lymphoma.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2006/049431

## A. CLASSIFICATION OF SUBJECT MATTER

**A61K 31/47(2006.01)i, A61K 31/4188(2006.01)i, A61P 35/02(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 8 A61K 31/47, A61K 31/4188, A61P 35/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
Korean Utility models and applications for Utility models since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
eKIPASS(KIPO) "((toll and receptor) or TLR) and lymphoma and non-hodgkin"

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US2004-162309 A1 (3M INNOVATIVE PROPERTIES COMPANY) 19 Aug. 2004 See page 8, paragraphs 99 - 104.	1-7, 9-25
X	US2004-091491 A1 (3M INNOVATIVE PROPERTIES COMPANY) 13 May 2004 See page 3, paragraphs 35 - 43.	1-8
A	US2004-141950 A1 (3M INNOVATIVE PROPERTIES COMPANY) 22 Jul. 2004 See pages 3, paragraph 42 - page 5, paragraph 61; page 8, paragraphs 91 - 96.	1-8

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
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Date of the actual completion of the international search  20 JUNE 2007 (20.06.2007)	Date of mailing of the international search report  <b>20 JUNE 2007 (20.06.2007)</b>
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Name and mailing address of the ISA/KR   Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer  YANG, In Soo  Telephone No. 82-42-481-5049
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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2006/049431**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004-162309 A1	19.08.2004	None	
US 2004-091491 A1	13.05.2004	AU 2004252409 A1 CA 2535338 A1 EP 1653959 A2 JP 2007500210 T2 US 2004265351 A1 WO 200518555 A3	06.01.2005 03.03.2005 10.05.2006 11.01.2007 30.12.2004 08.12.2005
US 2004-141950 A1	22.07.2004	None	